Remarks

The Office Action mailed 27 January 2005 has been received and reviewed. Claims 30-33, 37, 44, 45, and 67-70 having been amended, and claims 71-73 having been added, the pending claims are claims 30-33, 35-42, and 44-73, with claims 35, 36, 46-66 being withdrawn for being restricted to a non-elected invention. Support for new claims 71-73 is found, for example on pages 28 - 29, lines 1 - 4. Reconsideration and withdrawal of the rejections are respectfully requested.

Allowed Claims

Applicants thank the Examiner for notification that claims 30-33 contain allowable subject matter.

Objections

The Examiner objected to claims 30-33, 44, 45, 69, and 70 for recitation of "sequence SEQ ID NO:22" and/or "sequence SEQ ID NO:21" for lack of the word "of" between "sequence" and "SEQ." Applicants have amended the claims to address the Examiner's concern.

The 35 U.S.C. §112, First Paragraph, Rejection

The Examiner maintained the rejection of claim 70 under 35 U.S.C. §112, first paragraph, as containing new subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner alleged that claim 70 includes "the nucleic acid molecule . . . .or an immunogenic subunit or immunogenic fragment thereof," and that there is no descriptive support for "immunogenic subunit" or "immuogenic fragment" of the nucleic acid molecule in the instant specification, as originally filed. Applicants respectfully traverse the rejection.

Applicants previously amended claim 70 in the response mailed 1 November 2004, deleting the phrase "or an immunogenic subunit or immunogenic fragment thereof" where it applied to nucleic acids. The phrase "an avian *E. coli* Iss polypeptide or an immunogenic fragment or immunogenic subunit" remains in the claim, but in this case the immunogenic fragments or subunits are of the peptide rather than the nucleic acid. Applicants further note that an identical phrase is present in claims 37 and 68, which have not been rejected for containing new matter. As support for immunogenic fragments or immunogenic subunits of an avian *E. Coli* Iss polypeptide are supported by the originally filed specification (see pages 47-49), Applicants respectfully request that this rejection under 35 U.S.C. §112, first paragraph be withdrawn. As fragments and subunits are not indefinite with regard to the polypeptide, Applicants also request that the rejection of claim 70 under 35 U.S.C. §112, second paragraph, be withdrawn as well.

The Examiner rejected claims 37-42, 44, 45, and 67-70 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. More specifically, the Examiner alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicants respectfully traverse the rejection.

The Examiner appeared to be basing the lack of enablement rejection on several perceived problems. First, the Examiner states that "it is unlikely that the nucleic acid molecule alone as claimed in some of the claims, i.e., naked DNA, without an appropriate promoter, would express an Iss polypeptide or an immunogenic fragment or subunit of the polypeptide in any host." Second, the Examiner states that "[t]here is absolutely no evidence within the instant specification that the naked nucleic molecule as recited somehow got expressed ... to produce an Iss polypeptide, or an immunogenic fragment or subunit thereof, which induced 'some

therapeutic benefit or effect so as to result in an immune response that inhibits or prevents a septicemic disease' in the avian or mammalian subject." Third, the Examiner states that "gene therapy is unpredictable and complex wherein one of skill in the art may not necessarily be able to introduce and express an *Iss* nucleic acid or a part thereof in the cells of an avian or mammalian host[.]" In the interest of clarity, Applicants address each of these issues separately below.

The Examiner rejected claims 37-42, 44, 45, and 67-70 for not being enabled in part based on the Examiner's expectation that Iss polypeptide would not be expressed in the absence of a promoter. Applicants respectfully disagree, as only a very low level of expression of the polypeptide is needed to generate an immunogenic response. However, in the interest of furthering prosecution, applicants have amended claims 67-70 to include a promoter operably linked to the nucleic acid molecule used to express the Iss polypeptide. With regard to claims 37-42, 44, and 45, Applicants note that claim 37 recites the "nucleic acid further comprises at least one regulator sequence or control sequence operably linked to the nucleotide sequence." Control sequences are defined within the specification on page 28, lines 4-6 as "DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism." As claim 37 thus includes DNA sequences necessary for the expression of the coding sequence, and claims 38-42, 44, and 45 depended directly or indirectly on claim 37, all of the claims indicated by the Examiner, as amended, refer to either use of a promoter or control region to enhance expression of the encoded polypeptide, and thus should be found to be enabled in this aspect.

The Examiner further states that the claimed immunogenic composition is required to provide some therapeutic benefit or effect, and that therapeutic use is not enabled by the specification. Applicants respectfully note that applicants defined an immunogenic composition to encompass various means of stimulating antibody formation, and not as requiring a therapeutic benefit. In this regard, Applicants note that definition of "immunogenic

composition" on page 43, lines 23-28, defines an immunogenic composition not only in an *in vivo* context, but also as "a composition or preparation administered in an amount effective ... so as to result in the production of antibodies to a virulent complement resistant avian *E. Coli* isolate, or polypeptide or peptide employed as an immunogen." This notion is further reinforced by the disclosure which describes the preparation of antibodies to immunogenic Iss polypeptides, on pages 39 to 43 of the specification, for non-therapeutic applications such as, for example, diagnostic agents. Thus, the claimed immunogenic composition is not required to provide a therapeutic benefit or effect; rather, immunogenicity within the specification is defined both in the therapeutic and non-therapeutic context of stimulating antibody formation.

Applicants further note that the present claims are not directed to methods of therapeutic use *per se*, but merely to the immunogenic composition itself. In this regard, Applicants must disagree with part of the Examiner's statement on page 5 of the recent office action, that "the invention is related to an 'immunogenic composition' comprising a nucleic acid molecule, i.e., a DNA vaccine." While one aspect of the invention is an immunogenic composition comprising a nucleic acid molecule, Applicants do not equate this with a DNA vaccine, and respectfully request that the Examiner avoid conflating these terms in analysis of the claims.

In support of the notion that the composition claims of the present invention are enabled, Applicant directs the Examiner to Example O: Vaccines, as described in the "USPTO 35 U.S.C. 112, First Paragraph, Enablement Training Manual (1996)", which is attached herewith, labeled as Exhibit A. The example describes an application that provides a surface protein from *Lysobacteria erythrosis* which was isolated and used to generate antibodies. While noting that claims for vaccines in this example should not be allowed, in part due to a reference teaching that no vaccines for erythrosis are know, the example further notes that claims to a composition comprising the claimed peptide and a carrier would overcome the rejection. As the present claims are also directed to a composition, albeit to one including a nucleic acid molecule encoding the peptide rather than the peptide itself, the present claims are enabled based on

application of the USPTO's own training guidelines, which make a clear distinction between claims to compositions and claims to vaccines.

Finally, the Examiner's third argument was that one skilled in the art might not be able to introduce and express an *Iss* nucleic acid in the cells of an avian or mammalian host because gene therapy is unpredictable and complex. At the outset, Applicants note that while gene therapy is a complex endeavor, Applicants are not claiming a method of gene therapy. Furthermore, Applicants are not claiming a DNA vaccine. As noted above, the USPTO makes a clear distinction between immunogenic compositions and vaccines, and Applicants are claiming compositions. However, Applicants would agree that the invention described by Applicants relates to DNA vaccines, as DNA vaccination utilizes immunogenic compositions. As DNA vaccines are related to immunogenic compositions, and the Examiner has expressed concern regarding gene therapy, Applicants discuss the differences between DNA vaccines and gene therapy, below. However, Applicant respectfully requests that the Examiner keep in mind that the present claims are directed to immunogenic compositions, not DNA vaccines.

There are a number of distinct differences between DNA vaccines and gene therapy. For example, the Examiner notes, based on information provided in the review article by Phillips, that the two major challenges of gene therapy are to delivery DNA to target tissues and then express protein at therapeutic levels for the desired length of time. Neither of these issues, however, are a major obstacle for DNA vaccines. With regard to targeting tissues, a DNA vaccine generally does not have to be targeted to any particular tissue. Rather, it can be delivered anywhere within the body that an immune response can be provoked. Given the lack of importance of targeting, DNA vaccines are generally delivered to the muscle or skin, as these are readily accessible and are relatively harmless sites should significant inflammation occur in response to the vaccine. The expression issue is also much less of a problem for DNA vaccines, as transient expression is all that is necessary (and generally all that is desired) to provoke an immune response. A high level of expression is generally not necessary, as the immune system

is acutely sensitive, but when higher levels of expression are needed, the quantity of DNA delivered can be easily increased. Finally, a significant problem for gene therapy is the induction of an immune response to the newly expressed protein. Rather than being a problem, this is precisely the desired outcome for a DNA vaccine.

Current literature also supports the notion that DNA vaccines are an established technology where current work is directed to solving particular aspects of the technology rather than determining whether or not they can work at all. See, for example, Kim et al., Veterinary Microbiology 101, 39 (2004), Verfaillie et al., Vaccine 22, 1640 (2004), and Lasaro et al., Infection and Immunity 72, 6480 (2004), which have been included in a supplemental IDS associated with this response. Kim et al. demonstrates effective immunization against infectious bursal disease virus in chickens using DNA vaccines. Verfaillie et al. demonstrates an increased immune response using DNA vaccines in pigs to prevent neonatal enterotoxigenic *E. Coli* infection, and Lasaro et al. demonstrates the use of DNA vaccine priming to provide a protective immune response against *Salmonella* using administration through the parenteral route. Taken together, these references clearly demonstrate that DNA vaccines are a mature technology, and that undue experimentation would not be needed to make and use the immunogenic compositions currently claimed.

For at least the reasons provided above, Applicants submit that the subject matter of the claims is described in the specification in such a way as to enable one skilled in the art to make and/or use the invention, and respectfully request that the rejection under 35 U.S.C. §112, first paragraph for lack of enablement be withdrawn.

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claims 37, 41, 67, and 68 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner alleged that claims

are vague and confusing because it is unclear which of two polypeptides provides antecedent basis for the limitation 'the polypeptide'. Applicants have amended the claims to address the Examiner's concern. The usage of "a polypeptide" and "an avian *E. Coli* Iss polypeptide" should now be clear, as these two parts of the claim are both distinguished by the grammatical indefinite articles "a" and "an," which introduce these two differing parts of the claim as discrete terms. Later reference in the claim to "the polypeptide" thus refers to the term earlier introduced as "a peptide," while later usage of the term "the avian *E. Coli* Iss polypeptide" refers to the term introduced as "an avian *E. Coli* Iss polypeptide."

The Examiner further rejected claim 67 based on confusion and/or lack of antecedent basis for the limitations "subunit" and "fragment." Applicants have amended the claim to address the Examiner's concern.

In light of Applicant's amendments, Applicants respectfully request that the rejections under 35 U.S.C. §112, second paragraph, be withdrawn.

Summary

It is respectfully submitted that the pending claims 30-33, 35-42, and 44-77 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to **Mail Stop Amendment**, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 27th day of April, 2005, at 10:44 a.m. (Central Time).

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